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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Goddard, et al.
Appl. No.	:	10/063,670
Filed	:	May 7, 2002
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Gary B. Nickol
Group Art Unit	:	1642

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This Declaration is being submitted to demonstrate that the enhancement of TNF-α levels described in Example 17 is significant, reproducible, and reliable and that the claimed polynucleotides are therapeutically useful.

2. I am an inventor on the above-identified patent application and am familiar with the specification and prosecution history.

3. I was responsible for performing the assay described in Example 17 of the specification which discloses that several PRO polypeptides stimulate TNF-α release in human blood. The assay was conducted as described in the specification. Briefly, 200 µl of human blood supplemented with 50mM Hepes buffer (pH 7.2) was aliquotted per well in a 96 well test plate. To each well 300µl of either the test PRO polypeptide in 50 mM Hepes buffer (at various concentrations) or 50 mM Hepes buffer alone (negative control) was added and the plates were incubated at 37°C for 6 hours. The samples were then centrifuged and 50µl of plasma was collected from each well and tested for the presence of TNF-α by ELISA assay.

4. The assay was conducted using well-accepted and established scientific procedures, and the results reported in Example 17 are reliable and reproducible. PRO polypeptides which are reported as positive in the assay stimulated the release of at least 50-fold and up to more than 300-fold more TNF-α than the control samples. This constitutes a significant amount of TNF-α, and because more than a trace amount of TNF-α was released, the PRO polypeptides reported as positive are useful as described below. In fact, because TNF-α is normally undetectable in human blood, the at least 50-fold enhancement referred to above was determined by introducing purified TNF-α into a control sample and measuring the minimal amount of TNF-α detectable using the assay conditions described above. Thus, the at least 50-fold enhancement is relative to the minimal detectable amount of TNF-α rather than to the undetectable amount of TNF-α in normal human blood.

5. One cannot extend the transient induction of TNF-α production by murine macrophage PU5-1.8 cells upon contact with PMA observed in Goeddel, D.V. et al. Cold Spring Harbor Symposia on Quantitative Biology 51:597-609 (1986) to infer that the polypeptides encoded by the claimed polynucleotides will necessarily induce transient production of TNF-α in human cells. In addition, in an *in vitro* analysis such as that conducted by Goeddel et al., all the cells are simultaneously contacted with the agent which enhances TNF-α production, thereby permitting any regulatory consequences of continuous stimulation to occur. Such *in vitro* assays are not comparable to *in vivo* therapy in which different groups of cells are periodically exposed to the stimulatory agent over time. Because different groups of cells will come in contact with the stimulatory agent over time, TNF-α production will be continuously stimulated in the therapeutic context. Accordingly, the transient expression of TNF-α observed upon continuous stimulation is not relevant to and does not detract from the therapeutic usefulness of the claimed polynucleotides.

6. In addition to the benefits of increasing TNF-α levels for treating certain conditions, other conditions, such as rheumatoid arthritis and Crohn's disease, may be treated by reducing TNF-α levels. For example, the drug Enbrel is a fusion between TNF-α receptors and an immunoglobulin which is used to treat rheumatoid arthritis by reducing TNF-α levels. Inhibition of polypeptides which enhance TNF-α production, such as the polypeptides encoded by the polynucleotides claimed in the above-identified application, is useful for treating such

conditions. Accordingly, the claimed polypeptides are useful targets for treating diseases resulting from elevated TNF-α levels.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: 8/03/05 By: Paul J. Sutton

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